Pestic. Sci. 1996, **46**, 37–47

Natural Products as Pesticides: Two Examples of Stereoselective Synthesis*

Thomas Früh,‡ Philippe Chemla, Jürg Ehrler & Saleem Farooq

R&D Crop Protection, Ciba-Geigy AG, 4002 Basel, Switzerland

(Received 22 May 1995; revised version received 16 June 1995; accepted 12 September 1995)

Abstract: The strategy and synthetic efforts leading to efficient stereoselective syntheses of thiangazole, a *tris*-thiazolinyl-oxazole metabolite isolated from *Polyangium spp.*, and of hydantocidin, a spironucleoside metabolite isolated from *Streptomyces hygroscopicus*, are discussed.

Key words: thiangazole, hydantocidin, natural product, pesticide, chirality, stereoselective synthesis.

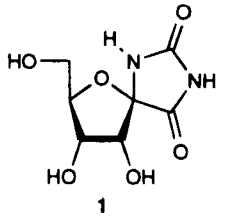
1 INTRODUCTION

In modern pest management there is a constant need for new crop protection chemicals. The most important reasons for this include resistance problems, high application rates needed with many older compounds and increasingly severe regulatory requirements. Methods which are used to identify new compounds with novel modes of action include random screening, analogue chemistry, biorational design and natural product chemistry. The search for natural products for crop protection serves the two main objectives of the development of new pesticides and the identification of new lead structures for chemical synthesis. Commercially successful examples of this approach include the insecticidal avermectins and the herbicidal molecule bialaphos (4-[hydroxy(methyl)phosphinoyl]-L-homoalanyl-L-alanyl-L-alanine), both fermentation products and also used as lead molecules. More recently, the strobilurins and the pyrrolnitrins gave rise to the development of the methoxyacrylate and the phenylpyrrole fungicides.

For a successful exploitation of the potential of a new natural product, a timely and sufficient supply of the material is very important. As many products derived from fermentation broths are difficult to purify and isolate on a large scale, an efficient stereoselective total synthesis is a valuable alternative to the fermentation optimization. Furthermore a total synthesis approach provides interesting intermediates which can be useful in a chemical derivatization program.

2 STEREOSELECTIVE SYNTHESIS OF (+)-HYDANTOCIDIN

(+)-Hydantocidin (**1**) (Fig. 1) is a natural spironucleoside isolated from *Streptomyces hygroscopicus* (Jensen, Waks. & Henrici strain) SANK 63854, by Sankyo,[1–3] from Tü-2474 by Ciba[4,5] and from A1491 by Mitsubishi Kasei[6] scientists. It exhibits an interesting profile of post-emergent herbicidal and plant growth regulatory activities. Structurally, it consists of a hydantoin unit and a ribose unit spiro-fused at the anomeric position. It was shown that (+)-hydantocidin is the only one of the 16 possible diastereoisomers at the four contiguous



1

Fig. 1. (+)-Hydantocidin.

* Based on a paper presented at the meeting 'Chirality in crop protection chemistry' organised by the Pesticide Group of the SCI and held at 14/15 Belgrave Square, London SW1X8PS on 7 March 1995.

‡ To whom correspondence should be addressed.

Pestic. Sci. 0031-613X/96/$09.00

stereogenic centres to be biologically active.[7,8] Because of these unusual structural features, and the potent herbicidal activity, considerable synthetic work has been invested in its preparation.[9–17] The low fermentation yield and the desire to avoid tedious separations of isomers prompted us to develop a stereocontrolled synthesis that would allow the preparation of sufficient material for more detailed biological investigations. Studies of the previous syntheses showed that the main challenge is the control of the configuration at the anomeric centre. This difficulty is compounded by the fact that the isomer bearing nitrogen in the α-position is thermodynamically more stable than the β-isomer.

Herein will be discussed three approaches towards a stereoselective synthesis of (+)-hydantocidin (Fig. 2). Our retrosynthetic analysis is based on the concept that hydantocidin should be mildly generated from a tricyclic isoxazolidine intermediate such as **2** (Fig. 2), thus 'freezing' the configuration at the anomeric centre until the end of the synthesis and avoiding any risk of epimerization. Obtaining this isoxazolidine intermediate involves a new oxygen-bridged intramolecular Vorbrüggen coupling reaction of a 5-hydroxylamine carbohydrate derivative (**4** or **7**; Fig. 2).[18–20] Three readily available chiral building blocks were examined as starting materials, i.e. D-glyceraldehyde (**6**; pathway **A**), D-ribonolactone (**8**; pathway **B**) and D-psicofuranose (**9**; pathway **C**).

2.1 Glyceraldehyde route A

D-Acetoneglyceraldehyde (**6**), a three-carbon unit binding block readily available from D-mannitol,[21] furnished one chiral centre which was used to control the three others: the anomeric position by internal cyclization of **4**, and the 2′,3′-diol by a hydroxylation of the olefinic tricyclic intermediate **3** from the less hindered bottom face. Introduction of the required *Z*-ketoolefin was envisaged by Wittig-Horner condensation of **6** with an α-ketoester phosphorane (Fig. 3).[22] In analogy with the well-documented reaction of methyl(triphenylphosphoranylidene)acetate with D-acetoneglyceraldehyde which yielded the *Z*-olefin **10** as major product when carried out in methanol at 0°C,[23] we assumed that phosphoranes stabilized by an α-ketoester would give the *Z*-adduct. Unfortunately, no reaction took place in methanol with the α-ketoester phosphorane reagents (Fig. 3, entry a) and only the *E*-olefin **12** was obtained when more vigorous conditions were applied. With alkylketophosphoranes (Fig. 3, entries b–d), the reaction led to mixtures (2:1) of *Z* and *E* olefins, easily separable by flash chromatography.

In spite of the moderate yields and stereoselectivity observed, compound **15** was employed as model for the acid-catalyzed cyclization step which was expected to generate an unsaturated hexofuranose. Different acids were employed to hydrolyse the isopropylidene group

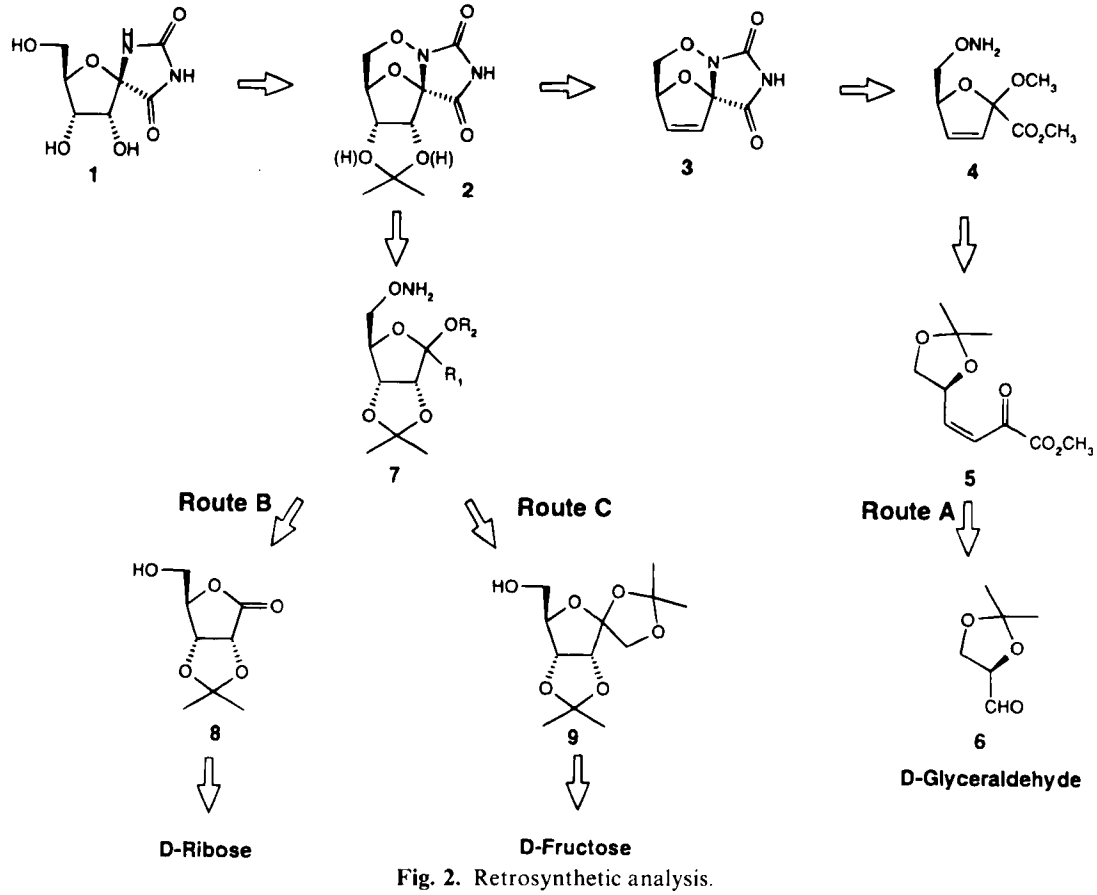
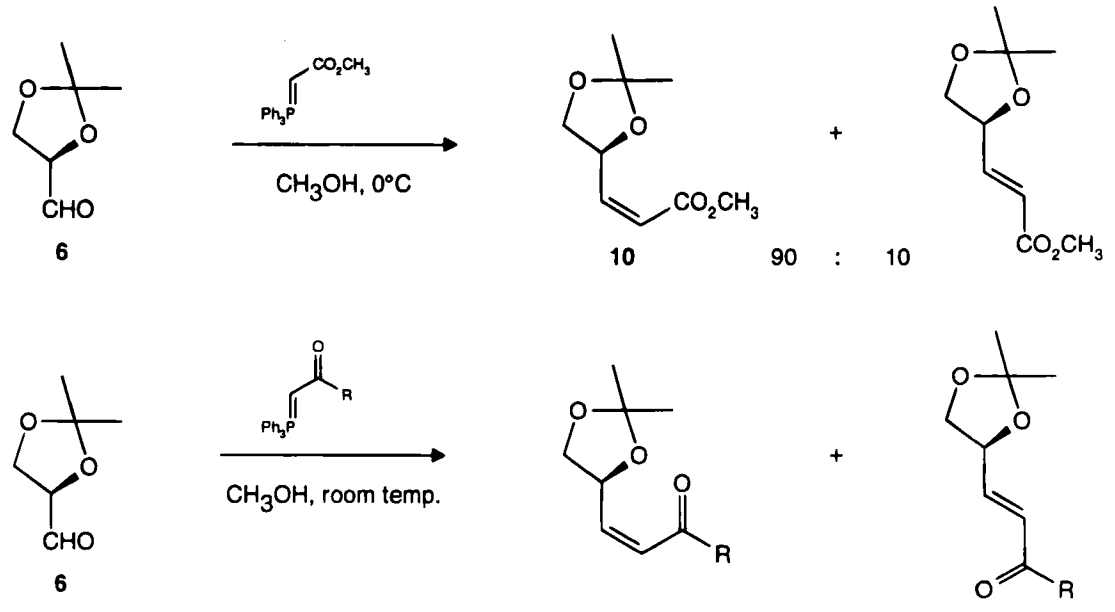


Fig. 2. Retrosynthetic analysis.



	R	Z/E	Compound	Yield (%)
a*	$CO_2C_2H_5$	0/100	**11/12**	75
b**	CH_2Br	66/34	**13/14**	60
c**	CH_2OCH_3	66/34	**15/16**	60
d**	CH_2OPMB	66/34	**17/18**	70

(*) toluene, reflux; (**) CHOH, room temp.

Fig. 3. Wittig-Horner reactions of α-keto-phosphoranes with D-glyceraldehyde (**6**).

and effect the ring closure, but only the furan **19** was isolated, and the intermediate diol was never observed (Fig. 4).

2.2 D-Ribonolactone route B (Fig. 5)

2,3-Isopropylidene-ribonolactone (**8**) derived from ribose[24] provides three of the four stereocentres of hydantocidin, and acetylene was used as a synthetic equivalent of the carboxylic function. Treatment of the lactone **20** with lithiated trimethylsilylacetylene, followed by addition of acetic anhydride afforded, after desilylation, the alcohol **21** as a single diastereoisomer. The hydroxyl group was then converted to the corresponding hydroxylamine **22** in a two-step sequence by substitution of the 5-OH by *N*-hydroxyphthalimide followed by cleavage with hydrazine.[25,26] Compound **22** was then submitted to the key acid-catalyzed intramolecular cyclization by treatment with sulfamic acid in nitromethane to give the heterocycle **23** in 65% yield, which rapidly equilibrated to the more stable cyclic oxime ether **24**. At this stage, all the chiral centres are in

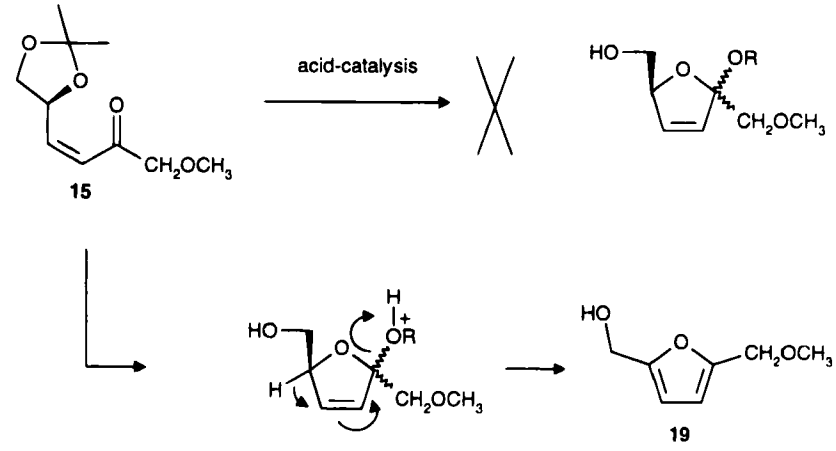


Fig. 4. Acid-catalyzed hydrolysis of compound **15**.

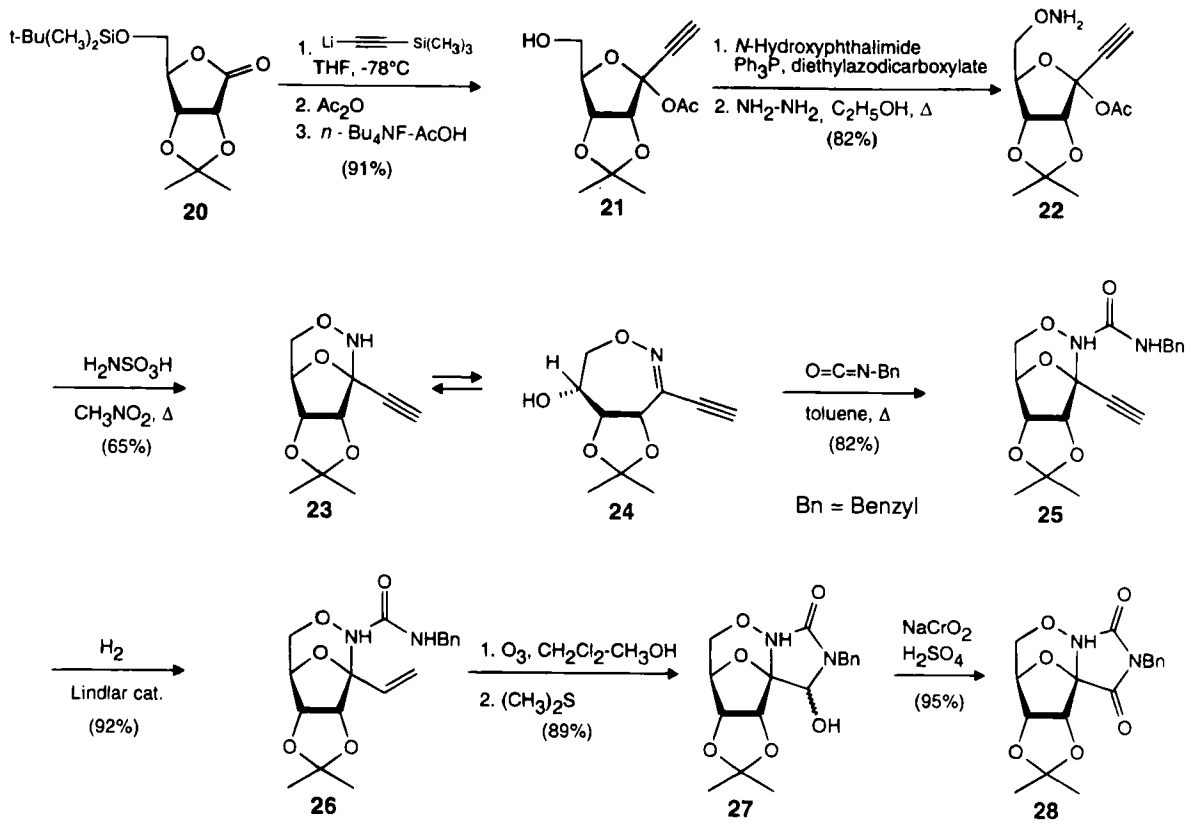


Fig. 5. The ribonolactone route.

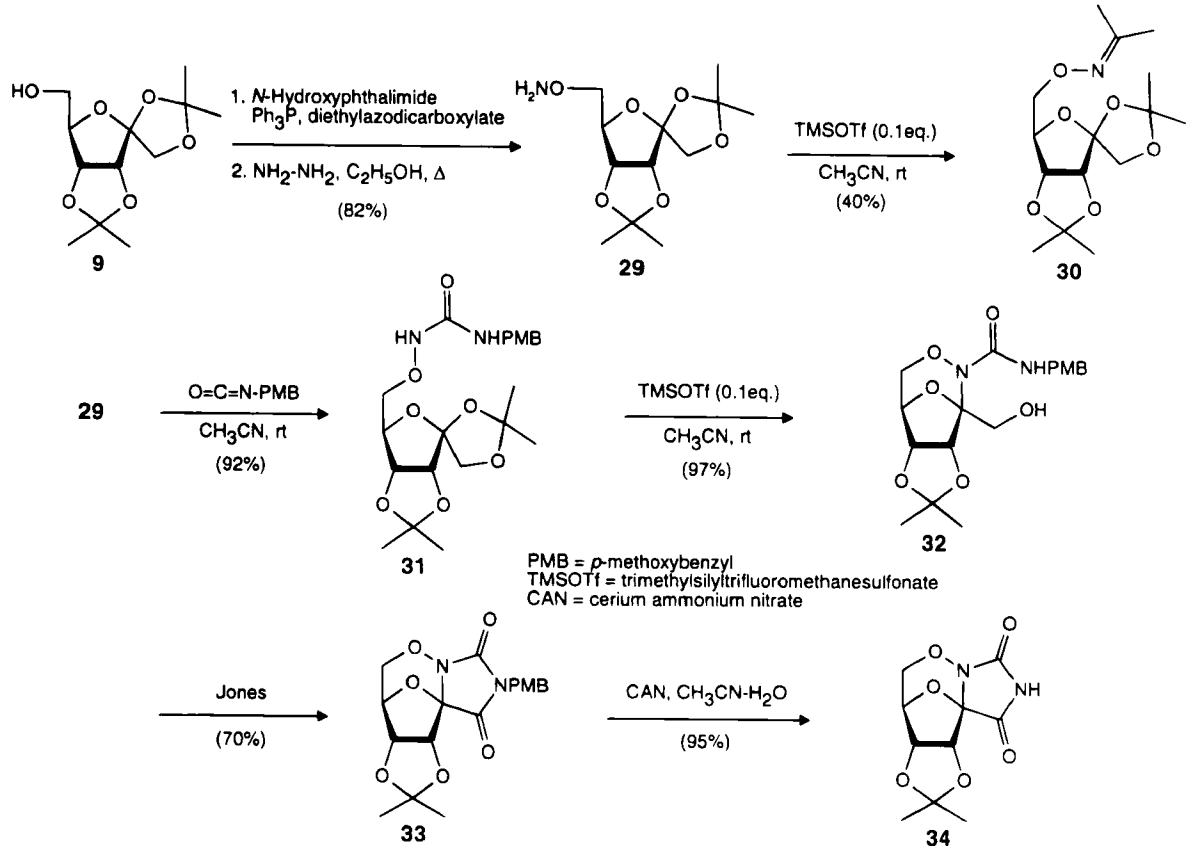


Fig. 6. The psicofuranose route.

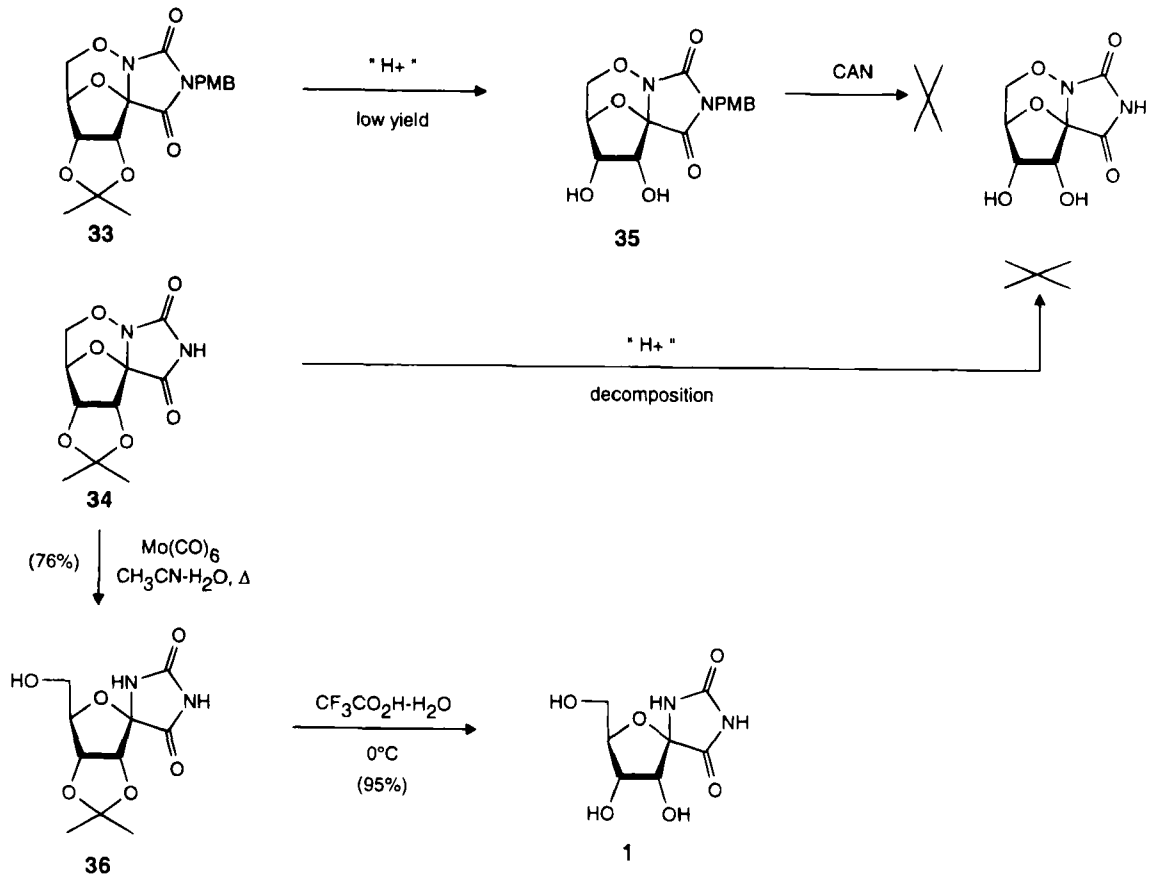


Fig. 7. Cleavage of the isoxazolidine ring.

place, and the nitrogen is fixed in the β-position. The hydantoin ring was then built in conventional manner, by oxidation of the tricyclic aminal **27** resulting from the ozonolysis of the olefin **26,** which was generated from **23** by acylation with benzyl isocyanate followed by a controlled hydrogenolysis. Although the synthesis was almost complete at this stage, unfortunately all attempts to cleave the imide nitrogen benzyl group by hydrogenolysis or metallic reduction failed.

Since it was necessary to replace the imide protecting group, 1,2:3,4-diisopropylidene-D-psicofuranose (**9**)[5,27] was found to be more appropriate to provide the required carbon framework and to lead also to our tricyclic heterocyclic key intermediate.

2.3 D-Psicofuranose route C (Fig. 6)

Conversion of the alcohol **9** to the corresponding hydroxylamine **29** was effected as described above. Initial attempts towards internal cyclization on the free hydroxylamine **29** catalyzed with trimethylsilyltriflate or sulfamic acid led only to the oxime **30**[28] and not to the cyclized compound as expected. In order to prevent the intermolecular acetone migration, compound **29** was converted to the corresponding *p*-methoxybenzylurea **31.** Treatment of the latter in the presence of a catalytic amount of trimethylsilyltriflate led to the heterocycle **32** in excellent yield. The configuration at C1 is thus fixed eliminating any risk of epimerization. Compound **32,** when treated with Jones reagent,[29] underwent oxidation and spontaneously cyclized to the tricyclic *N–O* bridged hydantocidin **33,** which after oxidative hydrolysis of the *p*-methoxybenzyl group with ceric ammonium nitrate (CAN),[30,31] afforded compound **34.**

Our first idea was to keep the *N–O* bridge to the end of the synthesis, but the isopropylidene protecting group in the tricyclic structures **33** and **34** proved to be extremely stable (Fig. 7). All attempts at hydrolysis of **34** failed. Although compound **35** was obtained in poor yield from **33,** removal of the *p*-methoxybenzyl group from **35** failed. Presumably because of the deactivation of the *N–O* bond by the carbamoyl group, the conventional cleavage methods (H_2-Pd/C, H_2-Ra/Ni,[32] Zn/AcOH,[33] Li-NH_3,[34] Al-Hg[35]) led only to decomposition. However, the organometallic complex $Mo(CO)_6$[36] proved to be the reducing agent of choice in this case, and the resulting 2',3'-isopropylidene-hydantocidin **36** (76%) was then deprotected in aqueous trifluoroacetic acid finally yielding the desired natural product in quantitative yield.

In conclusion, we have developed a new strategy to deliver specifically a nitrogen-containing moiety to the β-position at the anomeric centre of a ribose precursor, allowing multigram synthesis of hydantocidin with

complete stereocontrol. Following route **C**, hydantocidin was obtained in eight steps with an overall yield of 36% starting from psicofuranose (**9**).

3 STEREOSELECTIVE SYNTHESIS OF THIANGAZOLE

Thiangazole (**37**), a metabolite isolated from *Polyangium sp.*, strain PI3007, by Prof. G. Höfle *et al.*,[37] shows a variety of interesting biological effects such as antifungal, acaricidal and insecticidal activities, as well as HIV-1 inhibition.[38,39] It is related to a family of natural products known as tantazoles and mirabazoles, both isolated from terrestrial blue-green algae,[40–42] sharing a characteristic structural feature—a linear assembly of thiazoline rings and a terminal oxazole or thiazole ring. The synthesis of these novel products has recently received considerable attention. Syntheses of epididehydromirabazole A[43] [*S*-configuration of the ring-A stereocentre of didehydromirabazole A (**38**)], mirabazole B (**39**),[44] mirabazole C (**40**),[45,46] tantazole B (**41**)[47] and thiangazole (**37**)[48–50] have been reported (Fig. 8).

Thiangazole (**37**) consists basically of three different structural units: (i) a strongly hydrophobic styryl group, (ii) a consecutive assembly of three thiazoline rings, each of which is derived from (*R*)-2-methyl-cysteine and connected to its neighbouring groups at the 2- and 4-positions and (iii) a polar oxazole-4-carboxamide unit.

The goal of our synthetic efforts was the total synthesis of the natural product and its stereoisomers. We focused first on the synthesis of the subunits **A–D** (Fig. 9) which then led to the total synthesis of thiangazole.

The synthesis of the 2-phenyl-mono-thiazoline **44**, as well as of the corresponding *bis*- and *tris*-thiazolines was straightforward (Fig. 10). Condensation of the imino ether hydrochloride of benzonitrile (**42**) with ethyl L-cysteine hydrochloride, followed by methylation with lithium diisopropylamide/methyl iodide yielded the racemic ethyl 4-methyl-2-phenylthiazoline-4-carboxylate **44**, a suitable precursor of racemic ethyl 2-methylcysteine hydrochloride (rac.-**45**). The extension of **44** to the corresponding *bis*-thiazoline **46** was accomplished by coupling the thiazoline carboxylic acid chloride with rac.-**45** followed by cyclization with $TiCl_4$ according to Heathcock's method.[45] The two diastereomers of **46** were separated by flash chromatography on silica gel and extended to the corresponding *tris*-thiazolines using the same procedure.

Ethyl 4-methyl-2-phenylthiazoline-4-carboxylate (**44**) also served as a key intermediate in the preparation of

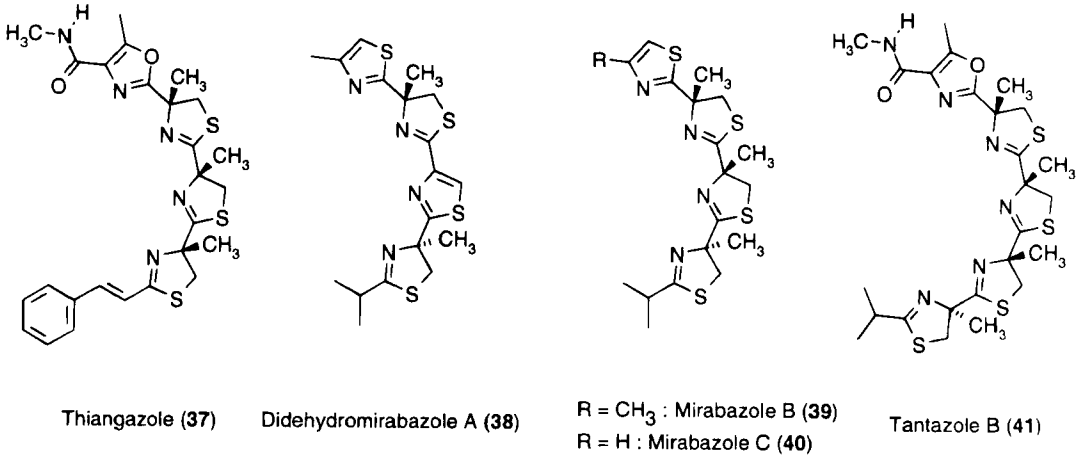


Fig. 8. Polythiazolines from natural sources.

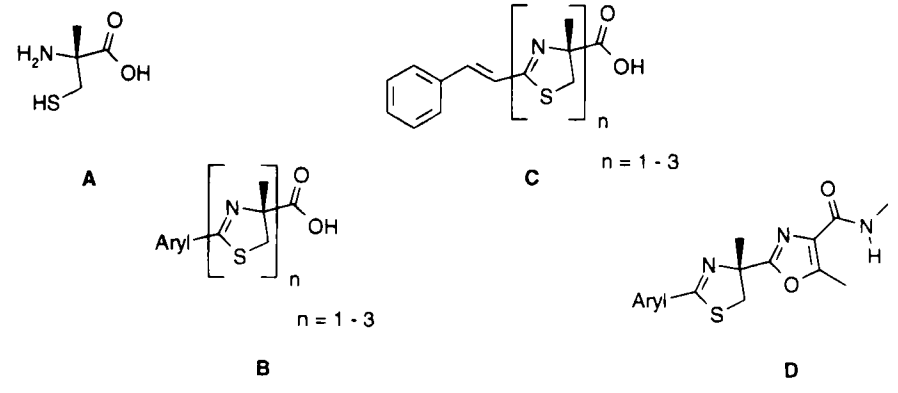


Fig. 9. Synthesis targets within the total synthesis of thiangazole (**37**).

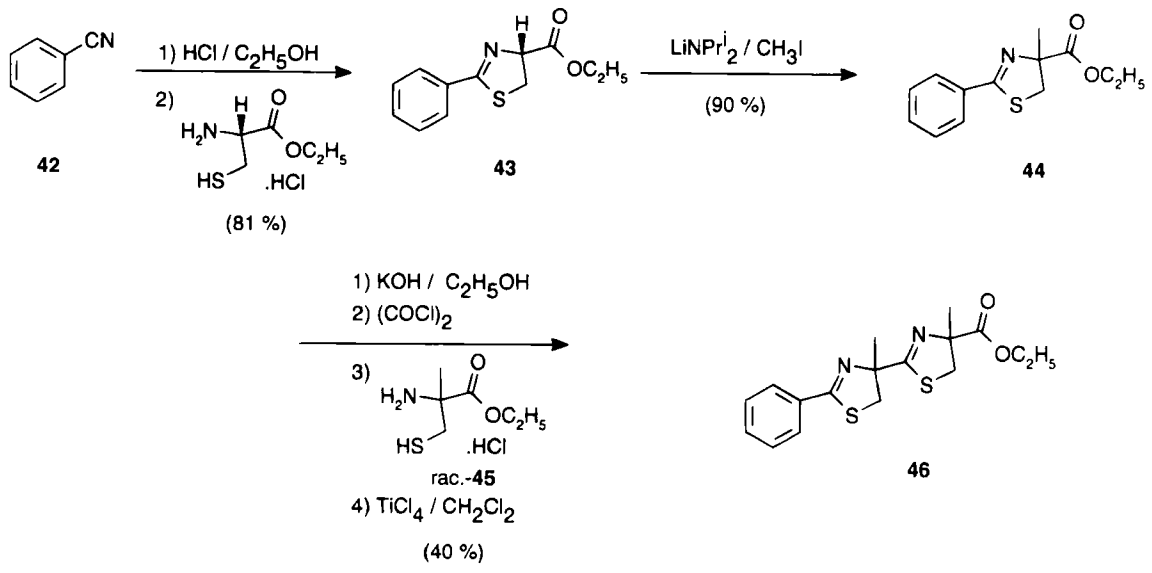


Fig. 10. Synthesis of the thiazolines **44** and **46.**

the two enantiomers of ethyl 2-methylcysteine and its hydrochloride (Fig. 11). Resolution of **44** by preparative HPLC on cellulose triacetate[51] yielded the enantiomerically pure thiazolines (*R*)- and (*S*)-**44**, which were hydrolysed and then esterified under acidic conditions to the corresponding ethyl 2-methylcysteine hydrochlorides (*R*)- and (*S*)-**45**. The determination of the absolute configurations was achieved by transformation of (*R*)- and (*S*)-**45** to the corresponding methyl S-benzyl-2-methylcysteine derivatives and comparison of the optical rotation values with literature data.[52] Pattenden *et al.*[53,54] have since published a multigram procedure for the synthesis of both (*R*)- and (*S*)-2-methylcysteine esters.

Various routes were investigated towards the synthesis of the thiazolinyloxazole units **E** (Fig. 12). Attempts at the cyclization of the thiazoline-4-carboxamides **48** and **49** using different methods[55-61] as well as the [3 + 2]-cycloaddition[62] of the thiazolinyl-nitrile **50** with ethyl 2-diazoacetoacetate in the presence of $[Rh(OAc)_2]_2$ were unsuccessful. However, a slight modification of Masamune's[63] procedure led to the desired oxazole **52** (Fig. 13). Reaction of the thiazolinyl-amide **51** with ethyl 3-bromo-2-oxobutyrate in the presence of cyclohexene oxide yielded the corresponding 4-hydroxyoxazoline which was dehydrated to the oxazole **52** by trifluoroacetic anhydride in pyridine.

During our studies towards the total synthesis of thiangazole (**37**), we found that the condensation of ethyl L-cysteine hydrochloride with the imino ether **53** (derived from cinnamamide) yielded, instead of the desired 2-styrylthiazoline **54**, mostly the seven-membered ring compound **55** arising from Michael addition of the mercapto group to the β-carbon atom of the cinnamoyl moiety (Fig. 14). To avoid these problems, we needed a 2-substituted thiazoline unit **F** which

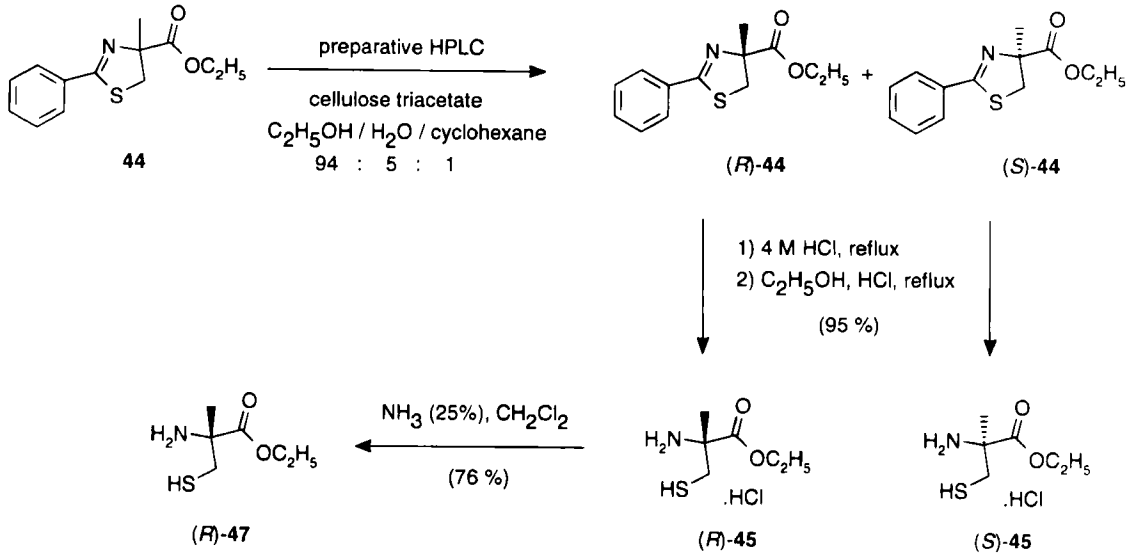


Fig. 11. Preparation of the enantiomerically pure ethyl 2-methylcysteine derivatives (R)-**45**, (S)-**45** and (R)-**47.**

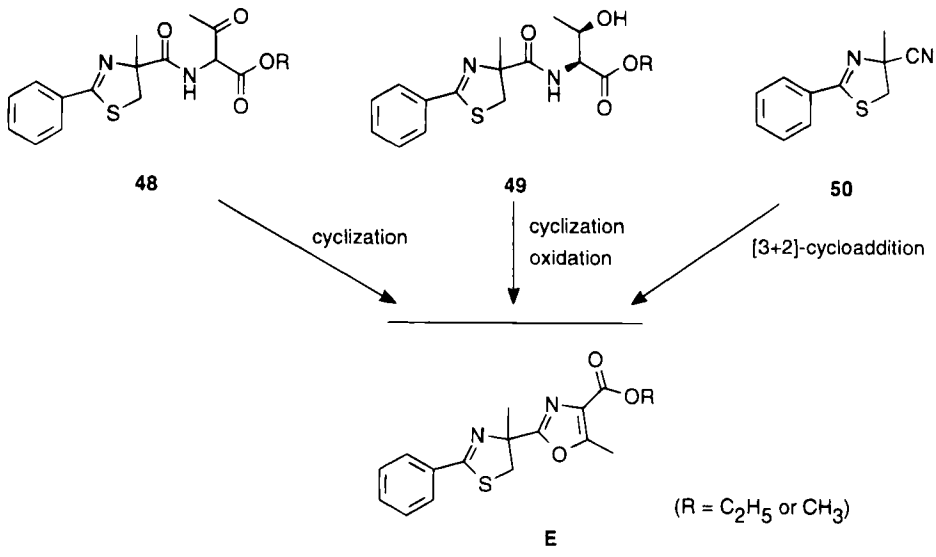


Fig. 12. Attempted routes towards the thiazolinyl-oxazole unit **E**.

allows the formation of the assembly of the three thiazoline rings followed by the introduction of the styryl group (Fig. 15).

The three alkyloxymethylthiazolines **57–59** were examined as precursors to the 2-formylthiazoline **56** into which the styryl function could be introduced by Wittig-type chemistry. However, all attempts at the deprotection of any of the derivatives **57–59** to the corresponding 2-hydroxymethyl- or 2-formylthiazoline failed. Attempts at the preparation of the 2-chloromethylthiazoline **60**, which we hoped to transform to the corresponding phosphonate, were also unsuccessful.

Starting from malonitrile or ethyl 2-cyanoacetate, respectively, the two thiazoline derivatives **61** and **62** were obtained in good yields. Knoevenagel condensation of **62** with benzaldehyde, followed by decarboxylation, led finally to the introduction of the styryl moiety; however, the extension of **62** to the corresponding *bis*-thiazoline failed at the selective saponification of the two ester functions.

As the thiazoline ring formation was facilitated by electron-withdrawing groups in the 2-position, we examined cyanomethyl diphenylphosphine oxide (**64**). Condensation of **64** with ethyl 2-methylcysteine hydrochloride gave the 2-phosphonomethylthiazoline **63** in good yield, which fulfilled all our requirements for the total synthesis.

The assembly of the *bis*- and *tris*-thiazolines **65** and

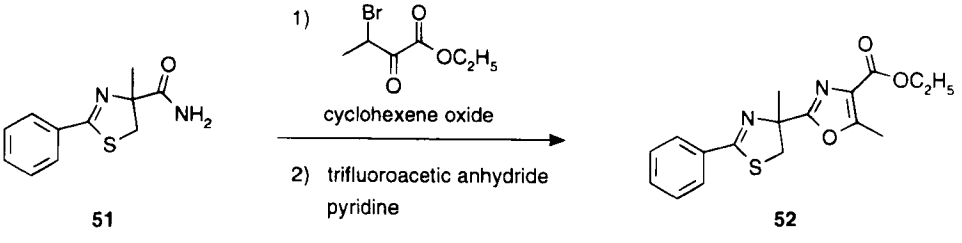


Fig. 13. Synthesis of the thiazolinyl-oxazole **52**.

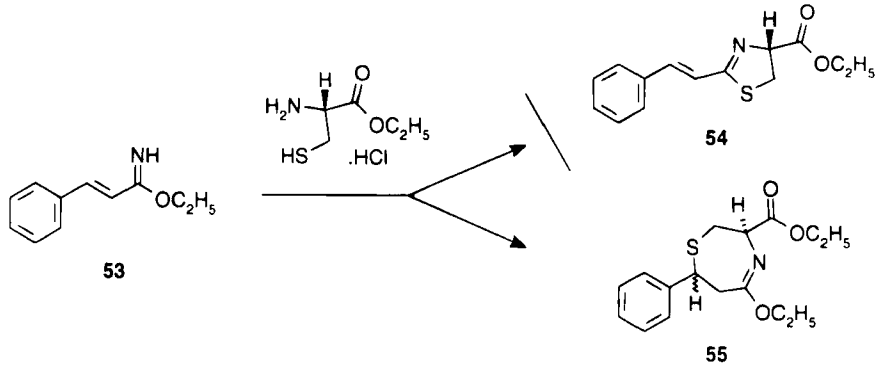


Fig. 14. Attempted synthesis of the 2-styryl-thiazoline **54**.

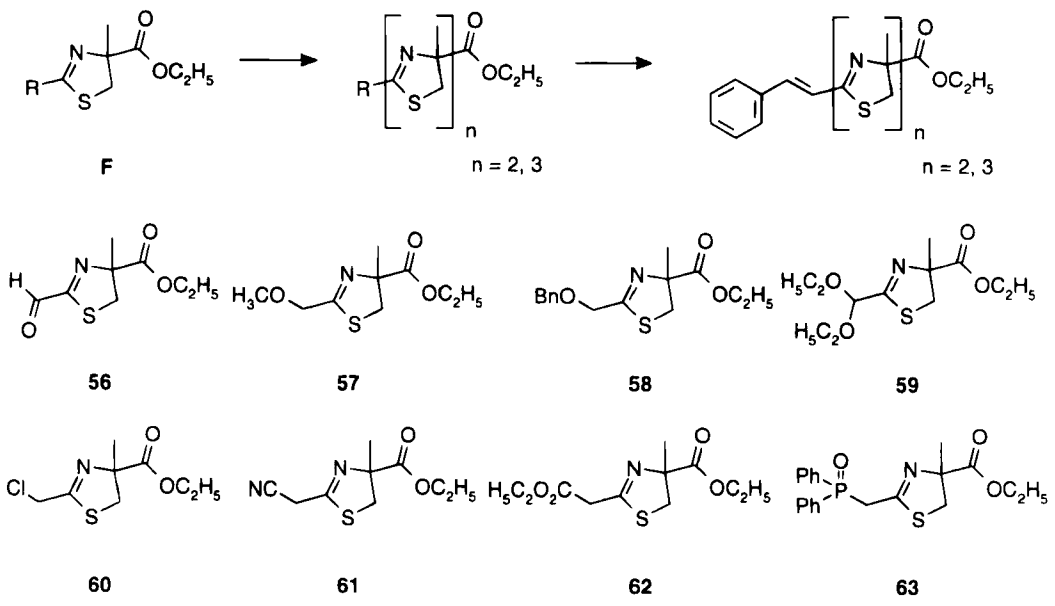


Fig. 15. Evaluated possible intermediates for thiangazole (**37**).

66, respectively, was accomplished *via* transformation to the corresponding acids, coupling with (*R*)-**47** in the presence of DCC and cyclization with $TiCl_4$ (Fig. 16). The styryl group was then introduced by a Wittig type reaction of the phosphine oxide **66** with benzaldehyde and the ester converted to the amide **67,** followed by the formation of the oxazole ring as described earlier, to give the oxazole ester. Saponification and transformation with the Ghosez reagent[64,65] to the acid chloride, followed by amide formation with methylamine produced thiangazole (**37**) as a white solid. In conclusion, thiangazole (**37**) has been synthesized in 16 steps from ethyl (*R*)-2-methylcysteine hydrochloride ((*R*)-**45**) with an overall yield of 0·9%.

4 CONCLUSIONS

The stereoselective syntheses of the natural products thiangazole and hydantocidin described here provide

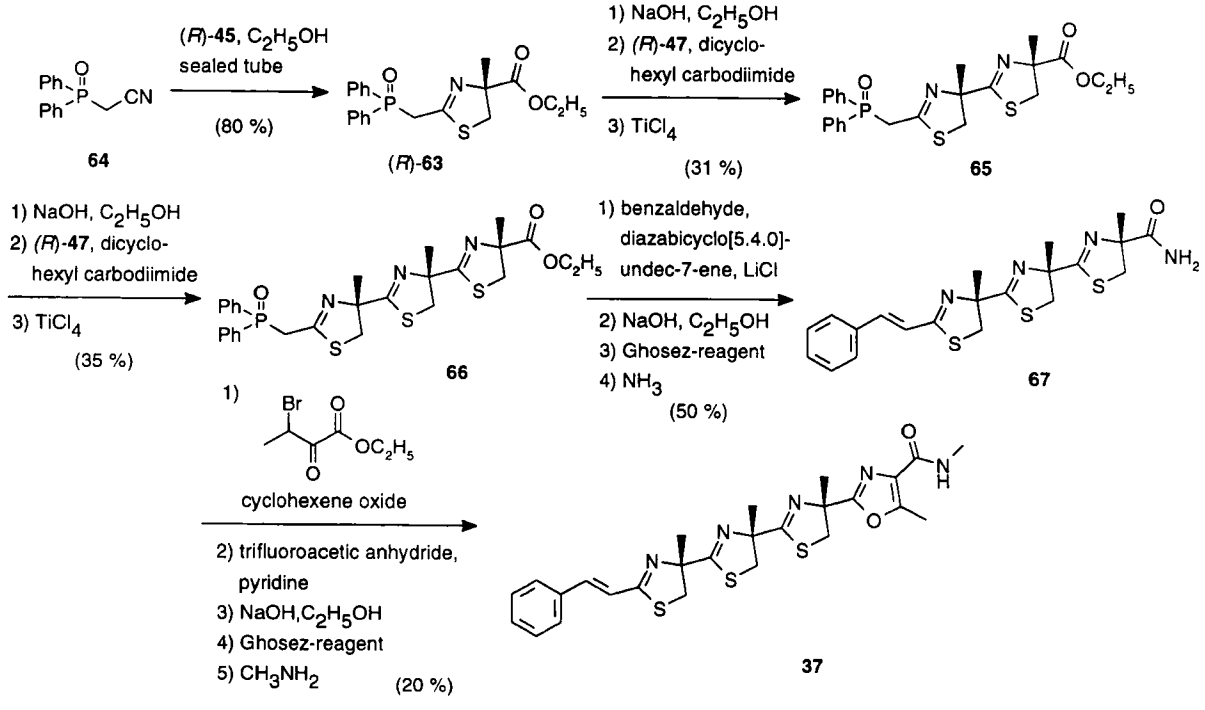


Fig. 16. Total synthesis of thiangazole (**37**).

easy access to the multigram quantities required for extensive biological profiling. In addition, the synthetic pathways possibly provide a series of interesting intermediates for derivatization programs.

ACKNOWLEDGEMENT

We would like to thank Prof. G. Höfle and Dr. J. P. Pachlatko for providing authentic material from the fermentation processes, C. Devonas, M. Fläschel, D. Härdi and H. Spörri for technical assistance with the laboratory work and Dr. A. C. O'Sullivan for reviewing the manuscript.

REFERENCES

1. Sankyo, *Eur. Pat. Appl.*, 0 232 572 A2, 19 August 1987.
2. Haruyama, H., Takayama, T., Kinoshita, T., Kondo, M., Nakajima, M. & Haneishi, T., *J. Chem. Soc. Perkin Trans.*, **1** (1991) 1637–40.
3. Nakajima, M., Itoi, K., Takamatsu, Y., Kinoshita, T., Okasaki, T., Kawakubo, K., Shindou, M., Honma, T., Tohjigamori, M., & Haneishi, T., *J. Antibiot.*, **44** (1991) 293–300.
4. Ciba Geigy AG, *Deutsches Pat.* 4129-616-A1, 10 Sept. 1990.
5. Fischer, H.-P., Nyfeler, R. & Pachlatko, J. P., *Proc. 1992 Agric. Biotech. Symp. on New Biopesticides*, Suwon (1992) pp. 17–54.
6. Mitsubishi Kasei Corp., *Jap. Pat.* 04222589-A, 19.12.1990.
7. Mio, S., Shiraishi, M., Sugai, S., Haruyama, H. & Sato, S., *Tetrahedron*, **47** (1991) 2121–32.
8. Mio, S., Ueda, M., Hamura, M., Kitagawa, J. & Sugai, S., *Tetrahedron*, **47** (1991) 2145–54.
9. Mio, S., Ichinose, R., Goto, K., Sugai, S. & Sato, S., *Tetrahedron*, **47** (1991) 2111–20.
10. Mio, S., Kumagawa, Y. & Sugai, S., *Tetrahedron*, **47** (1991) 2133–44.
11. Ciba Geigy AG, *Deutsches Pat.* 4129-728-A, 10 Sept. 1990.
12. Matsumoto, J., Kirihara, M., Yoshino, T., Kato, T. & Terashima, S., *Tetrahedron Lett.*, **34** (1993) 6289–92.
13. Chemla, P., *Tetrahedron Lett.*, **34** (1993) 7391–4.
14. Harrington, P. M. & Jung, M. E., *Tetrahedron Lett.*, **35** (1994) 5145–8.
15. Harrington, P. M. & Jung, M. E., *US Pat.* 5,354,868, 11 Oct. 1994.
16. Dondoni, A., Scherrmann, M.-C., Marra, A. & Délépine, J.-L., *J. Org. Chem.*, **59** (1994) 7517–20.
17. Sagami Chem. Res. Centre, *World Pat.* 9,413,685-A1, 11 Dec. 1992.
18. Vorbrüggen, H., Krolikiewic, K. & Bennua, B., *Chem. Ber.*, **114** (1981) 1234–55.
19. Vorbrüggen, H. & Krolikiewicz, K., *Angew. Chem., Int. Ed. Engl.*, **14** (1975) 421.
20. For review see: Pliml, J. & Prystas, M., *Adv. Heterocycl. Chem.*, **8** (1967) 115–42.
21. Dumont, R. & Pfander, Hp., *Helv. Chim. Acta*, **66** (1983) 814–23.
22. Le Corre, M., *Bull. Soc. Chim.*, (1974) 1951–5.
23. Häfele, B. & Jäger, V., *Liebigs Ann. Chem.* (1987) 85–7.
24. Kaskar, B., Heise, G. L., Michalak, R. S. & Vishnuvajjala, B. R., *Synthesis*, **11** (1990) 1031–2.
25. Grochowski, E. & Jurczak, J., *Synthesis* (1976) 682–4.
26. Tronchet, J. M. J., Schwarzenbach, D., Winter-Mihaly, E., Diamantindes, C., Likic, U., Galland-Barrera, G., Jorand, C., Pallie, K. D., Ojha-Poncet, J., Rupp, J., Moret, G. & Geoffroy, M., *Helv. Chim. Acta*, **65** (1982) 1404–11.
27. Prisbe, E. J., Smejkal, J., Verheyden, J. P. H. & Moffatt, J. G., *J. Org. Chem.*, **41** (1976) 1836–46.
28. Tronchet, J. M. J., Zosimo-Landolfo, G., Galland-Barrera, G. & Dolatshahi, N., *Carbohydr. Res.*, **204** (1990) 145–56.
29. Abushanab, E., Lee, D. Y. & Goodman, L., *J. Org. Chem.*, **40** (1975) 3376–8.
30. Yoshimura, J., Yamaura, M., Suzuki, T. & Hashimoto, H., *Chem. Lett.* (1983) 1001–2.
31. Yamaura, M., Suzuki, T., Hashimoto, H., Yoshimura, J. & Okamoto, T., *Bull. Chem. Soc. Jpn.*, **58** (1985) 1413–20.
32. Huisgen, R., Grashey, R., Seidl, H. & Hauck, H., *Chem. Ber.*, **101** (1968) 2559–67.
33. Wovkulich, P. M. & Uskokovic, M. R., *Tetrahedron*, **41** (1985) 3455–62.
34. Evans, D. A. & Sjorgren, E. B., *Tetrahedron Lett.*, **27** (1986) 3119–22. (Under these conditions the corresponding 'bridged' *N*-carbamoyl amide is obtained by the opening of the hydantoin ring.)
35. Keck, G. E. & Fleming, S. A., *Tetrahedron Lett.*, **19** (1978) 4763–6.
36. Cicchi, S., Goti, A., Brandi, A., Guarna, A. & De Sarlo, F., *Tetrahedron Lett.*, **31** (1990) 3351–4.
37. Jansen, R., Kunze, B., Reichenbach, H., Jurkiewicz, E., Hunsmann, G. & Höfle, G., *Liebigs Ann. Chem.* (1992) 357–9.
38. Gesellschaft für Biotechnologische Forschung mbH and Ciba Geigy AG, *World Patent Application* WO-A1-92/11258, 1992.
39. Jurkiewicz, E., Jansen, R., Kunze, B., Trowitzsch-Kienast, W., Forche, E., Reichenbach, H., Höfle, G. & Hunsmann, G., *Antiviral Chem. Chemother.*, **3** (1992) 189–93.
40. Carmeli, S., Moore, R. E., Patterson, G. M. L., Corbett, T. H. & Valeriote, F. J., *J. Am. Chem. Soc.*, **112** (1990) 8195–7.
41. Carmeli, S., Moore, R. E. & Patterson, G. M. L., *Tetrahedron Lett.*, **32** (1991) 2593–6.
42. Carmeli, S., Paik, S., Moore, R. E., Patterson, G. M. L. & Yashida, W. Y., *Tetrahedron Lett.*, **34** (1993) 6681–4.
43. Pattenden, G. & Thom, S. M., *Synlett.* (1992) 533–4.
44. Parsons, R. L. Jr & Heathcock, C. H., *Tetrahedron Lett.*, **35** (1994) 1383–4.
45. Walker, M. A. & Heathcock, C. H., *J. Org. Chem.*, **57** (1992) 5566–8.
46. Parsons, R. L. Jr & Heathcock, C. H., *Tetrahedron Lett.*, **35** (1994) 1379–82.
47. Fukuyama, T. & Xu, L., *J. Am. Chem. Soc.*, **115** (1993) 8449–50.
48. Boyce, R. J., Mulqueen, G. C. & Pattenden, G., *Tetrahedron Lett.*, **35** (1994) 5705–8.
49. Ehrler, J. & Farooq, S., *Synlett* (1994) 702–4.
50. Parsons, R. L. Jr & Heathcock, C. H., *J. Org. Chem.* **59** (1994) 4733–4.
51. Francotte, E. & Wolf, R. M., *Chirality*, **2** (1990) 16–31.
52. Groth, U. & Schöllkopf, U., *Synthesis* (1983) 37–8.
53. Pattenden, G., Thom, S. M. & Jones, M., *Tetrahedron*, **49** (1993) 2131–8.
54. Mulqueen, G. C., Pattenden, G. & Whiting, D. A., *Tetrahedron*, **49** (1993) 5359–64.
55. Cornwall, P., Dell, C. P. & Knight, D. W., *J. Chem. Soc. Perkin. Trans. 1* (1991) 2417–28.
56. Gordon, T. D., Singh, J., Hansen, P. E. & Morgan, B. A., *Tetrahedron Lett.*, **34** (1993) 1901–4.
57. Knight, D. W., Pattenden, G. & Rippon, D. E., *Synlett* (1990) 36–7.

58. Yokokawa, F., Hamada, Y. & Shioiri, T., *Synlett* (1992) 149–50.
59. Yokokawa, F., Hamada, Y. & Shioiri, T., *Synlett* (1992) 151–2.
60. Yokokawa, F., Hamada, Y. & Shioiri, T., *Synlett* (1992) 153–5.
61. Evans, D. A., Gage, J. R., Leighton, J. L. & Kim, A. S., *J. Org. Chem.*, **57** (1992) 1961–3.
62. Connell, R. D., Tebbe, M., Helquist, P. & Akermark, B., *Tetrahedron Lett.*, **32** (1991) 17–20.
63. Vaccaro, H. A., Levy, D. E., Sawabe, A., Jaetsch, T. & Masamune, S., *Tetrahedron Lett.*, **33** (1992) 1937–40.
64. Devos, A., Remion, J., Frisque-Hesbain, A.-M., Colens, A. & Ghosez, L., *J.C.S. Chem. Commun.* (1979) 1180–1.
65. Haveaux, B., Rens, M., Sidani, A. R., Toye, J. & Ghosez, L., *Org. Syntheses*, **59** (1980) 26–34.